IJPC PEER REVIEWED

Compatibility and Stability of Palonosetron Hydrochloride with Gentamicin, Metronidazole, or Vancomycin During Simulated Y-Site Administration

Thomas C. Kupiec, PhD
Michel Ben, MS
Analytical Research Laboratories
Oklahoma City, Oklahoma

Craig Trusley, PharmD, MS
Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey
Piscataway, New Jersey

Lawrence A. Trissel, BS, RPh, FASHP
TriPharma Research
Cashiers, North Carolina

ABSTRACT

Palonosetron hydrochloride is a relatively long-acting selective 5-HT3 receptor antagonist that has been approved for the prevention of chemotherapy-induced nausea and vomiting and is being evaluated for the prevention of postoperative nausea and vomiting. The objective of this study was to evaluate the physical and chemical stability of palonosetron hydrochloride 50 mcg/mL when mixed with gentamicin sulfate 5 mg/mL, metronidazole 5 mg/mL, or vancomycin hydrochloride 5 mg/mL during simulated Y-site administration. Duplicate samples of palonosetron hydrochloride with each of the anti-infectives were tested. Samples were stored and evaluated for up to 4 hours at room temperature. Physical stability was assessed by turbidimetric and particulate measurements and visual inspection. Chemical stability was assessed by high-performance liquid chromatography. All of the admixtures were clear and colorless when viewed in normal fluorescent room light and when viewed with a Tyndall beam. Measured turbidity and particulate content were low initially and remained low throughout the study. The drug concentration was unchanged in all of the samples tested. Palonosetron hydrochloride is physically and chemically stable with gentamicin sulfate, metronidazole, or vancomycin hydrochloride at the concentrations tested during simulated Y-site administration over 4 hours at ambient room temperature.

ACKNOWLEDGMENT

This study was supported by a grant from MGI PHARMA, Inc., Bloomington, Minnesota.

INTRODUCTION

Palonosetron hydrochloride (HCl) injection (Aloxi, MGI PHARMA, Inc.) is a relatively long-acting selective 5-HT3 receptor antagonist that has been approved for the prevention of chemotherapy-induced nausea and vomiting[1-4] and has recently completed phase III trials for the prevention of postoperative nausea and vomiting. Palonosetron HCl injection has been evaluated for compatibility with a number of chemotherapy and supportive care drugs,[5-19] and it may be administered with many other drugs by simultaneous or sequential Y-site administration, including anti-infective drugs.

The purpose of this study was to evaluate the physical and chemical stability of undiluted palonosetron HCl 50 mcg/mL when mixed during simulated Y-site administration with gentamicin sulfate 5 mg/mL diluted in 5% dextrose, metronidazole infusion 5 mg/mL, or vancomycin HCl 5 mg/mL diluted in 5% dextrose.

MATERIALS AND METHODS

Materials

Palonosetron HCl injection (Lot HPA 109; MGI PHARMA, Inc., Bloomington, Minnesota) was supplied by the manufacturer. Gentamicin sulfate (Lot 200559; American Pharmaceutical Partners, Schaumburg, Illinois), metronidazole (Lot P180810; Baxter Healthcare, Deerfield, Illinois), and vancomycin HCl (Lot 33321DD; Hospira, Lake Forest, Illinois) injections were obtained commercially. The infusion solution 5% Dextrose Injection USP (Lot C647339; Baxter Healthcare) in polyvinylchloride bags also was obtained commercially. The palonosetron HCl reference standard (Lot H-0492; Helsinn Chemicals SA, Lugano, Switzerland) was supplied by MGI PHARMA, Inc., and was used without further purification. Reference standards for gentamicin (Lot 41-227-DK; Hospira), metronidazole (Lot SF1670; Spectrum Chemical, Gardena, California), and vancomycin (Lot 015K08251; Sigma-Aldrich, St. Louis, Missouri) also were obtained commercially. The acetonitrile and other mobile phase components were suitable for high-performance liquid chromatographic (HPLC) analysis. The water used was HPLC grade (Barnstead Nanopure, Dubuque, Iowa) and was prepared immediately before use.

Allen et al reported that the mixing of an intravenous fluid in an administration set with a secondary additive through a Y-injection site occurs in a 1:1 ratio.[20] To simulate this inline mixing, duplicate samples were prepared by mixing 7.5-mL samples of undiluted palonosetron HCl 50 mcg/mL with 7.5-mL samples of gentamicin sulfate 5 mg/mL in 5% dextrose, metronidazole 5 mg/mL undiluted, or vancomycin HCl 5 mg/mL in 5% dextrose in colorless 15-mL borosilicate glass screw-cap culture tubes (Kimble, Division of Owens-Illinois, Toledo, Ohio) with polypropylene caps (Kimble) as described elsewhere.[21] The individual drug admixtures were filtered through appropriate 0.22-mcm filters (Millex-GS; Millipore Corporation, Bedford, Massachusetts) into the tubes. All manipulations were carried out in a Class 100 biological safety cabinet.

Physical Stability

The physical stability of the admixtures was assessed by visual examination and by measuring turbidity and particle size and content.[21-23] The sample tubes had been previously triple-washed in HPLC-grade water and dried. To minimize the effects of scratches and imperfections in the glass, a thin layer of silicone oil was applied to the exterior of each tube. Visual examinations were performed in normal diffuse fluorescent room light with the unaided eye and by using a high-intensity monodirectional light (Tyndall beam; Dolan-Jenner Industries, Woburn, Massachusetts).

The turbidity of each sample was measured by a color-correcting turbidimeter (Model 2100AN; Hach Company, Loveland, Colorado). Triplicate determinations were made on each of the samples. A light obscuration particle sizer/counter (Model 9703; Hiac-Royco, Division of Pacific Scientific Company, Grants Pass, Oregon) was used to quantify particles in the samples in the 2.04-mcm to 112-mcm range (the validated detection limits of the particle sizer/counter) and to verify the absence of unacceptable amounts of microparticulates 4 hours after mixing. Particulate determinations also were made in triplicate. Physical instability was defined as visible particulate matter, haze, color change, or a change (increase or decrease) in measured turbidity of 0.5 nephelometric turbidity unit (NTU) or more.

High-Performance Liquid Chromatographic Analysis

The drug concentrations in each admixture were determined by stability-indicating HPLC assay methods. The details of the analytical methods used in this study are cited in Table 1. The palonosetron HCl analytical method was provided by the drug manufacturer.[24] The analytical methods for gentamicin sulfate and vancomycin HCl were adapted from the methods of Allen et al[25] and Vaughan and Poon, respectively.[26] The analytical method for metronidazole was developed in our laboratory. All of the methods were validated in our laboratory to verify their suitability for this testing. Two high-performance liquid chromatographs, a Hewlett-Packard Series 1050 and a Hewlett-Packard Series 1100 (both supplied by Agilent Technologies, Palo Alto, California) were used for analysis of the palonosetron HCl drug mixtures. Each high-performance liquid chromatograph consisted of a multisolvent delivery pump, autosampler, and photodiode array detector. The systems were controlled and integrated by a personal computer with chromatography management software (HPLC ChemStation Version A.09.03; Agilent Technologies). Triplicate HPLC determinations were performed on duplicate samples of each test admixture.

The analytical methods for each of the drugs were demonstrated to be stability-indicating by accelerated degradation. The sample solutions were mixed separately with 1 N hydrochloric acid, 1 N sodium hydroxide, or 3% hydrogen peroxide, and subjected to heating. Loss of the intact drugs was observed, and the degradation product peaks or other drug peaks did not interfere with the peak of the intact subject drug.

The initial concentrations of palonosetron HCl and the three anti-infective agents were defined as 100%, and subsequent sample concentrations were expressed as a percentage of the initial concentration. Drug stability was defined as a concentration of not less than 90% of the initial drug concentration remaining in the admixtures.

RESULTS AND DISCUSSION

All of the samples of palonosetron HCl admixtures with the three anti-infective agents were initially clear and colorless in normal fluorescent room light and when viewed with a Tyndall beam. The samples were essentially without haze, having measured turbidities of less than 0.17 NTU. Changes in turbidity for the samples were minor throughout the study, less than 0.02 NTU. Measured particulates of 10 mcm or larger were few in number in all samples and remained so throughout the observation period. The admixtures remained colorless throughout the study.

The results of the HPLC analysis for each of the test drugs are shown in Tables 2 through 4. No loss of palonosetron HCl occurred in any of the drug admixtures over 4 hours. Similarly, no loss of the anti-infective drugs occurred in 4 hours. Therefore, palonosetron HCl is compatible with and stable in admixtures with the three anti-infective agents at the concentrations tested during simultaneous or sequential Y-site administration.

Previous stability and compatibility tests of palonosetron HCl during simulated Y-site administration with a variety of parenteral medications have demonstrated that palonosetron HCl is a very stable drug.[5-19] None of the previous studies have found any loss of palonosetron HCl during the testing interval. In this series of tests of simulated Y-site administration with three anti-infective agents, palonosetron HCl once again demonstrated stability. The previous studies reported that most of the tested drugs also were stable and compatible in the presence of palonosetron HCl. When palonosetron was mixed with methylprednisolone sodium succinate, however, free methylprednisolone was precipitated when combined with palonosetron,[12] most likely because of the acidic pH (pH 4.5 to 5.5)[1] of the palonosetron HCl injection. While all of the anti-infective drugs in the present study were stable and compatible in admixtures with palonosetron HCl, it is useful to keep in mind that drugs that demonstrate such pH-dependent incompatibilities may present compatibility problems if combined with or administered simultaneously with acidic drug solutions such as palonosetron HCl.

CONCLUSION

Palonosetron HCl is physically and chemically stable when mixed with gentamicin sulfate, metronidazole, or vancomycin HCl during simulated Y-site administration.

REFERENCES

1. Aloxi [palonosetron hydrochloride package insert]. Bloomington, MN: MGI PHARMA, Inc. January 2006.
2. Gralla R, Lichinitser M, Van Der Vegt S et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: Results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. *Ann Oncol* 2003; 14(10): 1570–1577.
3. Eisenberg P, Figueroa-Vadillo J, Zamora R et al. Improved prevention of moderate CINV with palonosetron, a pharmacologically novel 5-HT3 receptor antagonist: Results of a phase III, single-dose trial vs dolasetron. *Cancer* 2003; 98(11): 2473–2482.

Table 1. High-Performance Liquid Chromatographic Analytical Methods Used for Palonosetron and the Anti-infective Drugs.

	Palonosetron[a]	Gentamicin[b]	Metronidazole[c]	Vancomycin[d]
Mobile phase	720 mL Water 280 mL Acetonitrile 0.67 mL Trifluoroacetic acid	5 g Hepatanesulfonic acid sodium salt 250 mL Water 50 mL Glacial acetic acid 700 mL Methanol	1.03 g Potassium phosphate monobasic 750 mL Water 50 mL Acetonitrile 200 mL Methanol	1.54 g Ammonium acetate 900 mL Water 100 mL Acetonitrile
Diluent	Mobile phase	16% (1 g O-Phthalaldehyde in 5 mL methanol and 95 mL 0.4 M boric acid, pH adjusted to 10.4 with 6 N sodium hydroxide, mixed with 2 mL thioglycolic acid, pH readjusted to 10.4 with 6 N sodium hydroxide) 84% Isopropyl alcohol	200 mL Water 800 mL Methanol	Purified water
Column	Zorbax SB-C8[e] (250 × 4.6 mm, 5 mcm)	Phenomenex Luna-C18[f] (150 × 4.6 mm, 5 mcm)	Phenomenex Gemini-C18[f] (150 × 4.6 mm, 5 mcm)	Phenomenex Gemini-C18[f] (150 × 4.6 mm, 5 mcm)
Flow rate	1.0 mL/minute	2.0 mL/minute	1.5 mL/minute	2.0 mL/minute
Detection	254 nm	330 nm	316 nm	214 nm
Sample				
Injection volume	50 mcL	20 mcL	10 mcL	10 mcL
Retention times				
Palonosetron	9.3 minutes	1.9 minutes	Not detected	Not detected
Gentamicin	2.5, 3.4, 4.0 minutes	3.0 minutes (C1), 10.1 (C1a), 13.1 (C2a), 15.9 (C2) minutes	Not detected	Not detected
Metronidazole	3.7 minutes	—	2.7 minutes	Not detected
Vancomycin	3.4 minutes	—	Not detected	3.2 minutes
Decomposition products	Multiple 2.3 to 2.5, 3.1, and 3.3 minutes	1.2, 1.9, 2.3, 4.0, 4.5, 5.1, 5.7, 6.5, 7.1, 8.2 minutes	1.4, 1.6 minutes	Multiple 1.0 to 2.5, 3.8, 4.1, 4.4, 5.5, 5.8 minutes

[a]Precision: Mean ± standard deviation (SD) (n = 9) diluted in mobile phase to a nominal concentration of 25 mcg/mL; percent relative standard deviation (RSD) was 0.08%. Standard curve range was 6.25 to 31.25 mcg/mL. The correlation coefficient was >0.9999.
[b]Precision: Mean ± SD (n = 9) diluted to a nominal concentration of 500 mcg/mL; percent RSD was 0.24%. Standard curve range was 125 to 627 mcg/mL for gentamicin C1, C1a, C2, and C2a in aggregate. The correlation coefficient was >0.9999.
[c]Precision: Mean ± SD (n = 9) diluted to a nominal concentration of 100 mcg/mL; percent RSD was 0.20%. Standard curve range was 25 to 125 mcg/mL. The correlation coefficient was >0.9997.
[d]Precision: Mean ± SD (n = 9) diluted in mobile phase to a nominal concentration of 200 mcg/mL; percent RSD was 0.16%. Standard curve range was 50 to 250 mcg/mL. The correlation coefficient was >0.9999.
[e]Supplied by Agilent (Palo Alto, California).
[f]Supplied by Phenomenex (Torrance, California).

4. Aapro MS, Grunberg SM, Manikhas GM et al. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. *Ann Oncol* 2006; 17(9): 1441–1449.
5. Trissel LA, Xu QA. Physical and chemical stability of palonosetron HCl in 4 infusion solutions. *Ann Pharmacother* 2004; 38(10): 1608–1611.
6. Trissel LA, Zhang YP. Physical and Chemical stability of palonosetron HCl with cisplatin, carboplatin, and oxaliplatin during simulated Y-site administration. *J Oncol Pharm Pract* 2004; 10(4): 191–195.
7. Trissel LA, Zhang Y. Palonosetron hydrochloride compatibility and stability with doxorubicin hydrochloride and epirubicin hydrochloride during simulated Y-site administration. *Ann Pharmacother* 2005; 39(2): 280–283.
8. Trissel LA, Xu QA. Physical and chemical stability of palonosetron hydrochloride with topotecan hydrochloride and irinotecan hydrochloride during simulated Y-site administration. *IJPC* 2005; 9(3): 238–241.

Table 2. Stability of Palonosetron Hydrochloride with Various Drugs During Simulated Y-Site Administration.

	Percentage of Initial Concentration Remaining[a]			
Time (Hours)	*#1*	*#2*	*#1*	*#2*
	Palonosetron Hydrochloride[b]		*Gentamicin Sulfate*[c]	
1	100.52 ± 0.09	99.96 ± 0.13	101.23 ± 0.14	99.84 ± 0.09
4	100.19 ± 0.06	99.60 ± 0.15	100.12 ± 0.16	100.01 ± 0.10
	Palonosetron Hydrochloride[d]		*Metronidazole*[e]	
1	100.53 ± 0.80	99.75 ± 0.13	99.83 ± 0.24	100.36 ± 0.04
4	99.90 ± 0.18	100.01 ± 0.41	99.51 ± 0.04	100.56 ± 0.07
	Palonosetron Hydrochloride[f]		*Vancomycin Hydrochloride*[g]	
1	100.06 ± 0.06	99.89 ± 0.02	99.57 ± 0.03	99.93 ± 0.23
4	99.79 ± 0.13	99.29 ± 0.00	100.35 ± 0.18	99.02 ± 0.08

[a]Mean ± standard deviation for triplicate determinations of duplicate samples.
[b]Initial concentrations of the duplicate samples were 26.75 and 26.78 mcg/mL.
[c]Initial concentrations of the duplicate samples were 5.26 and 5.26 mg/mL.
[d]Initial concentrations of the duplicate samples were 24.37 and 25.05 mcg/mL.
[e]Initial concentrations of the duplicate samples were 2.67 and 2.60 mg/mL.
[f]Initial concentrations of the duplicate samples were 26.92 and 27.27 mcg/mL.
[g]Initial concentrations of the duplicate samples were 4.907 and 4.907 mg/mL.

9. Trissel LA, Xu QA. Physical and chemical compatibility of palonosetron hydrochloride with lorazepam and midazolam hydrochloride during simulated Y-site administration. *IJPC* 2005; 9(3): 235–237.
10. Trissel LA, Zhang Y. Physical and chemical stability of palonosetron hydrochloride with fluorouracil and with gemcitabine hydrochloride during simulated Y-site administration. *IJPC* 2005; 9(4): 320–322.
11. Xu QA, Trissel LA. Physical and chemical stability of palonosetron hydrochloride with cyclophosphamide and ifosfamide during simulated Y-site administration. *Am J Health Syst Pharm* 2005; 62(19): 1998–2000.
12. Trissel LA, Zhang Y, Xu QA. Physical and chemical stability of palonosetron hydrochloride with dacarbazine and methylprednisolone sodium succinate during simulated Y-site administration. *IJPC* 2006; 10(3): 234–236.
13. Xu QA, Trissel LA. Stability of palonosetron hydrochloride with paclitaxel and docetaxel during simulated Y-site administration. *Am J Health Syst Pharm* 2004; 61(15): 1596–1598.
14. Trissel LA, Trusley C, Ben M et al. Physical and chemical stability of palonosetron hydrochloride with five narcotics during simulated Y-site administration. *Am J Health Syst Pharm* [In press].
15. Ben M, Trusley C, Kupiec TC et al. Physical and chemical stability of palonosetron hydrochloride with glycopyrrolate and neostigmine during simulated Y-site administration. *IJPC* [In press].
16. Trusley C, Ben M, Kupiec TC et al. Physical and chemical stability of palonosetron with metoclopramide and promethazine during simulated Y-site administration. *IJPC* 2007; 11(1): 82–85.
17. Trusley C, Ben M, Kupiec TC et al. Compatibility and stability of palonosetron hydrochloride with four neuromuscular blocking agents during simulated Y-site administration. *IJPC* 2008; 12(2): 156–160.
18. Kupiec TC, Trusley C, Ben M et al. Physical and chemical stability of palonosetron hydrochloride with five common parenteral drugs during simulated Y-site administration. [In press.]
19. Ben M, Trusley C, Kupiec TC et al. Palonosetron hydrochloride compatibility and stability with three β-lactam antibiotics during simulated Y-site administration. *IJPC* 2007; 11(6): 520–524.
20. Allen LV Jr, Levinson RS, Phisutsinthrop D. Compatibility of various admixtures with secondary additives at Y-injection sites of intravenous administration sets. *Am J Hosp Pharm* 1977; 34(9): 939–943.
21. Trissel LA, Bready BB. Turbidimetric assessment of the compatibility of taxol with selected other drugs during simulated Y-site injection. *Am J Hosp Pharm* 1992; 49(7): 1716–1719.
22. Trissel LA, Martinez JF. Turbidimetric assessment of the compatibility of taxol with 42 other drugs during simulated Y-site injection. *Am J Hosp Pharm* 1993; 50(2): 300–304.
23. Trissel LA, Martinez JF. Physical compatibility of melphalan with selected drugs during simulated Y-site administration. *Am J Hosp Pharm* 1993; 50(11): 2359-2363.
24. Palonosetron HCL IV Injection 0.05 mg/mL and 0.15 mg/mL end product test procedure. Minneapolis, MN: MGI PHARMA, Inc.; [Undated].
25. Allen LV, Stiles ML, Prince SJ et al. Stability of cefpirome in the presence of commonly used intensive care drugs during simulated Y-site injection. *Am J Health Syst Pharm* 1995; 52(21): 2427–2433.
26. Vaughan LM, Poon CY. Stability of ceftazidime and vancomycin alone and in combination in heparinized and nonheparinized peritoneal dialysis solution. *Ann Pharmacother* 1994; 28(5): 572–576.

Address correspondence to Lawrence A. Trissel, BS, RPh, FASHP, TriPharma Research, P.O. Box 265, Cashiers, NC 28717-0265.